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Principal Investigator	Principal Investigator Organization	Project Title	General Project Abstract
Alexander Parker	Mayo Clinic	The Molecular Epidemiology of Renal Cell Carcinoma	Renal cell carcinoma (RCC) is by far the most common form of kidney cancer. Of interest, the number of people diagnosed each year with RCC, as well as those who eventually die from this cancer, has been steadily increasing in the United States (and Florida) for more than three decades. Despite this, the underlying causes of RCC remain poorly understood. In our application, we propose to conduct a large case control study of RCC in order to improve our understanding of the causes of RCC. This project will be the result of a combined effort by investigators at two Florida academic medical institutions (Mayo Clinic and Moffitt Cancer Center) and will involve recruitment of 1,400 individuals with RCC and 1,400 controls with no history of cancer. Using data and tissue samples collected from these individuals, we will build on the current knowledge that smokers, obese individuals and those with a history of urinary tract infections are at increased risk of developing RCC. That is, we will test specific hypotheses regarding exactly how these factors work at the cellular level in the kidney to cause RCC. By doing so, we have the potential to enhance our understanding of how these common exposures increase a person's risk of RCC. As such, our findings could translate into new intervention strategies (i.e. better risk stratification, early detection, and/or chemoprevention) that would ultimately reduce the burden this cancer places on individuals and society at large.

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Charles Rosser	M. D. Anderson Cancer Center	A Multidisciplinary Approach to Improve Patient Outcome in Bladder Cancer - A Tobacco-Related Disease	Bladder cancer (BCa) is among the five most common malignancies worldwide. The major risk factor associated with the development of BCa is tobacco smoke. BCa cases for 2010 are estimated at 60,000, with estimated deaths at 12,700. Despite these figures, BCa remains a cancer that is poorly understood. There are currently several pressing issues regarding (1) how and why BCa develops, (2) what factors in the urine can be used to diagnosis or monitor BCa and (3) what novel therapies could be used alone or in combination to improve patient outcomes. In this application, we have assembled a collaborative team from a variety of medical and research fields in order to harness the incredible resources in Florida for the express purpose of addressing these pressing issues with regard to BCa. Our intention is to conduct five projects: one focused on a new therapeutic agent for BCa, one focused on new targets for drug development, one focused on determining new markers for early BCa detection, one focused on how smoking increases the risk of developing BCa and one focused on the effects of cigarette smoke extract on tumor growth. At the participating institutions, M.D. Anderson Cancer Center Orlando, H. Lee Moffitt Cancer Center, University of Miami School of Medicine, Mayo Clinic Florida and University of Central Florida, we have the resources, study personnel, and patient populations to complete the necessary tasks in a timely and successful manner.

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Jamie Fernandez	University of South Florida	Neuroendocrine Disruption and Nicotine Preference in a Rat Model of Postpartum Depression	Postpartum depression (PPD) is a devastating disease occurring in 10-15 percent of women. Women who suffer from PPD appear to be sensitive to postpartum hormonal changes. Further, of women who quit smoking during pregnancy, those who develop PPD are at an increased risk of smoking relapse. Animal models exhibiting both PPD and nicotine preference have not been studied and thus, the mechanistic relationship between the two is unknown. Studies investigating susceptibility to drug abuse have indicated that animals who respond to a novel open field with high activity (HR) exhibit alterations in response to stress and a greater preference for nicotine compared with animals who respond with lower activity (LR). Thus, parallels between HR rats and rats exhibiting PPD suggest that the former may be used as a 'model' to study maternal behavior, susceptibility to depression, and increased nicotine preference. These studies will use differences between HR and LR rats to investigate PPD and nicotine dependence. It is predicted that postpartum, HR rats will exhibit both depression and a greater tendency to neglect their young as compared to LR rats. It is also anticipated that HR rats exhibiting signs of PPD will have higher nicotine preference, and that estrogen treatment will reduce this preference for nicotine. These studies will provide evidence on the etiology of PPD and a rationale for the use of estrogen replacement to prevent nicotine relapse during the postpartum period.

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Charles Saunders	Florida State University	Improving Surveillance Measures of Tobacco Use in Florida's Adolescent Population	The goal of this study is to determine what effect peer, familial and media influences have on adolescent smoking in order to improve the surveillance and evaluation component of Florida's youth anti-tobacco initiatives. Social influences are among the most important and consistent factors associated with adolescent smoking. However, the manner in which social influences manifest, and more importantly, how they interact in a population of adolescent smokers is not well understood. Therefore, this study will have three specific aims. Aim 1: Obtain detailed information over a three year period on the social influence of media, family and peers from a representative population of Florida adolescents. Aim 2: Determine the effect of social influences and the manner in which they interact on Florida's adolescent smokers and non-smokers using well-defined statistical techniques and measures from the social interaction/social network literature. Aim 3: Using the results from Aim 2 coupled with the current surveillance and evaluation of tobacco control program methodologies developed by the Centers for Disease Control and Prevention and World Health Organization, improve the current surveillance measures of adolescent smoking in Florida, particularly for subgroups based on gender, age and ethnicity.

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Dileep Yavagal	University of Miami	Intra-arterial Mesenchymal [Animal] Stem Cell Delivery in a Canine Model of Acute Ischemic Stroke	Millions of smokers are disabled or die as a result of stroke in the U.S. To date, the only FDA approved treatment for acute stroke is the clot-dissolving drug tissue plasminogen activator (tPA). However, tPA must be administered within 3 hours of the onset of an ischemic stroke, which makes it a viable treatment for less than 15% of stroke patients. Thus, new therapies for acute stroke with extended therapeutic windows are badly needed. Recently, multiple types of stem cells have been shown to be beneficial for the treatment of stroke in experimental studies in mice and rats. Mesenchymal stem cells (MSCs) derived from the adult non-hematopoietic compartment of the bone marrow hold the greatest promise for use in human clinical trials in stroke due to several desirable clinical attributes, including the absence of ethical concerns and the cells' immune privileged status. Studies of MSCs delivered via catheter into the carotid artery after stroke has proven beneficial in the rodent models. However, there are no studies of MSCs in large animal models of stroke. This is crucial prior to launching human clinical trials, as biologically the large animal brain is much closer to the human brain. Thus, in the current application our main goal is to test safety and effectiveness of intra-carotid delivery of four escalating doses of MSCs given 36- 48 hours after induction of ischemic stroke in a large animal model.

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Robert Gillies	Moffitt Cancer Center & Research Institute	Radiomics of Lung Cancer Screening	This year, 160,000 Americans will die of lung cancer, and worldwide, annual deaths will exceed 10 million by the year 2030. Significant improvements can come from earlier detection. Recently, the National Lung Cancer Screening Trial, NLST, with over 53,000 participants, showed that participants screened annually with computed tomographic (CT) had a significant survival benefit. CT scans detect “suspicious nodules”, which have to then be biopsied to determine if they are cancerous. 25% of all patients had biopsies and, of these, over 90% were not cancer, meaning that the biopsy could have been avoided. Furthermore, of the cancers detected by annual screening, 80% were aggressive and advanced when first discovered. This suggests that there is a subpopulation of patients who were at higher risk and perhaps should be screened at more frequent intervals. In this study, we will re-analyze the 75,136 CT scans in the NLST database at higher resolution with a specialized computer program developed for this purpose. These data will be used to determine if computer measurement of small, nearly invisible changes (“Radiomics”) will be able to identify those patients at higher risk, and thus who need to be scanned more frequently; and those who are lower risk, who may not need biopsies and who may be scanned less frequently. It is important to note that, if this method proves successful, it will improve the diagnostic power of CT scans with no increase in costs.

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Stephen Coombes	University of Florida	Cortical and Subcortical Brain Function in Chronic Stroke	Tobacco use doubles the risk for stroke and leads to strokes occurring a decade earlier than in non-tobacco users. Every year in the US, approximately 795,000 people suffer a new or recurrent stroke. At 6-months post stroke 26% of stroke survivors need help with daily activates such as grooming, dressing, and cooking. These activities are compromised because stroke often disrupts the areas of the brain that control hand function. Understanding brain function during visually guided movements after stoke is important because assessment and rehabilitation approaches involve visually guided movements. The current proposal will first characterize how stroke influences brain activity during a visually guided grip task, and second, will manipulate visual feedback during the task to increase activity in specific regions of the affected motor system. Increased activity in the affected motor system has been associated with better recovery. Our long term goal is to use the findings from this proposal to develop novel treatments that engage affected motor circuits to optimize recovery after stroke. The current proposal is consistent with the goals of the James and Esther King Biomedical Research program because our findings will: 1) improve the health of Floridians with stroke by developing novel approaches to optimize rehabilitation, 2) expand the foundation of biomedical knowledge related to brain function in stroke, and 3) attract additional funding from outside the state.

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Brian Lally	University of Miami	Genomic Prediction Models of Lung Cancer Survival and Treatment Response	Lung cancer is the leading cause of cancer-related deaths in the United States. Tobacco contributes to 90% of lung cancer. The health burden of tobacco will only be exacerbated while underserved minority populations have higher smoking rates. Our and others' data clearly demonstrated that African Americans have the worst survival. The overall survival and quality of life are associated with tumor stage and poorly defined intrinsic factors. We hypothesize that smoking may contribute to racial/ethnic disparities in lung cancer treatment response and mortality because African Americans: (1) are more susceptible to tobacco-related lung cancer risk and (2) have more advanced lung cancer tumors. To achieve the long-term overarching goals in reducing disparities in lung cancer mortality and quality of life, our primary goal is to evaluate racial/ethnic disparities in treatment response and quality of life in three racial/ethnic groups of lung cancer patients, African Americans, Hispanic Whites, and non-Hispanic Whites. We will test the hypothesis that worse lung cancer outcomes are associated with smoking and somatic mutations (changes in DNA that cause cancer), that have greater impact in underserved populations. With a large tri-racial/ethnic population, promising preliminary data, high-throughput technology, and skilled multidisciplinary collaboration, we are in an exceptional position to conduct the proposed research.

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Lirong Peng	Moffitt Cancer Center & Research Institute	Regulations and functions of Tip60 and hMOF	Cells are exposed to DNA damage during normal development processes. These damages are dangerous to cells if they are not repaired or eliminated. Mammalian cells have an intricate machinery of DNA damage response (DDR) to repair and eliminate damaged DNA. Aberration of DDR will impair the integrity of the genome and lead to tumorigenesis. Understanding the underlying mechanisms of DDR is critical for prevention, diagnosis, and treatment of cancer. Histone acetylase (Tip60 and hMOF) and deacetylase (SIRT1) critically regulate DDR. However, how Tip60/hMOF synergistically acts with SIRT1 in DDR is unclear. Though Tip60/hMOF and SIRT1 are aberrantly expressed in multiple types of cancer, their exact roles in the development of lung cancer remain unclear. I found that SIRT1 dynamically deacetylates Tip60/hMOF and inhibits its enzymatic activity and apoptotic function. Overexpression of Tip60/hMOF or depletion of SIRT1 results in higher drug resistance in lung cancer cells. Therefore, I propose to examine the regulation and functions of Tip60/hMOF in lung cancer with the following aims. 1) Examine roles of SIRT1-mediated deacetylation of MOF/Tip60 in DDR. 2) Dissect the mechanisms and machineries by which SIRT1 dynamically interacts with Tip60/hMOF during DDR. 3) Explore the roles of Tip60/hMOF and SIRT1 in the tumorigenesis of lung cancer. This study will give new insights to the development of new therapeutic treatments for lung cancer.

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Lina Shehadeh	University of Miami	Modulation of miR-30e in Nicotine-Enhanced Atherogenic and Osteogenic Pathways	Cigarette smoking is as a major risk factor for atherosclerotic vascular disease, including coronary artery disease and stroke. When risk factors are present, atherosclerosis is initiated early as evidenced by fatty streaks on the vessel wall that in turn promote a cascade of responses in the underlying endothelium and smooth muscle (SM) layers. Vascular smooth muscle cells (VSMCs) are especially implicated in the pathogenesis of atherosclerosis and therefore, identification of pathways that mediate the smoking-related dysfunction of these cells and their responses to cholesterolemia and fatty streaks may unravel new therapeutic targets. Nicotine, the addictive compound in cigarette smoke, exacerbates neointimal and atherosclerotic plaque formation. Using a bioinformatics approach, we determined that the host gene NFYC of microRNA-30e is repressed by smoking in human lungs and blood, and validated nicotinic regulation of miR-30e targets in VSMCs in culture. The long term goal is to develop an RNA molecule (miR-30e) into a therapeutic agent for smoking-related vascular disease. The specific aims of the proposal are to 1) determine the action of miR-30e on nicotine-enhanced cholesterol biosynthesis, vascular plaque formation, and SM differentiation, 2) determine the mechanism by which miR-30e regulates SM differentiation, and 3) determine the mechanism by which miR-30e regulates osteogenic differentiation of mesenchymal stem cells with nicotine treatment.

Jose Silva	University of Miami	Involvement of hypothalamic non-protein coding RNAs in the metabolic response to prenatal nicotine exposure in offspring	Although cigarette smoking during pregnancy is associated with adverse fetal, obstetrical, and developmental outcomes, 15–20% of all women smoke throughout the duration of pregnancy. Recent human epidemiological studies have shown a strong relationship between maternal smoking and subsequent obesity and type 2 diabetes in the offspring. Of the 4000 chemicals in cigarette smoke, animal studies suggest that prenatal nicotine exposure (PNE) to nicotine alone may result in postnatal metabolic alterations associated with obesity and type 2 diabetes. These studies further suggest that PNE has long-lasting effects on hypothalamic body weight regulation. Animal studies indicate that PNE alters the functioning of hypothalamic neurons regulating food intake and body weight, in particular that of Pro-opiomelanocortin (POMC) producing neurons. We hypothesize that PNE predisposes to late-onset metabolic disturbances that are associated with gene expression changes in POMC neurons. We will resort to a mouse model mimicking human maternal nicotine abuse from adolescence throughout pregnancy to determine whether PNE alters body weight regulation and gene expression in hypothalamic POMC neurons of offspring. These studies will also focus on expression changes of long non-protein coding ribonucleic acids (long ncRNAs) capable of regulating gene expression. We hope to identify new egulatory mechanisms involved in the metabolic response to prenatal nicotine exposure in offspring.

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Hoshang Unwalla	University of Miami	Restoring the Mucociliary clearance enhancing properties of inhaled beta-2-agonist bronchodilators in chronic bronchitis.	Cigarette smoking leads to chronic bronchitis (CB) and COPD and is characterized by depressed mucociliary clearance (MCC). Understanding the pathophysiological mechanisms that lead to impaired MCC in chronic bronchitis is important to public health, especially if we can identify new treatment regimens for a disease with few therapeutic options. COPD is treated with & beta-2-adrenergic receptor agonists available in an aerosolized form for inhalation. Apart from smooth muscle relaxation, beta-2-agonists like albuterol and salmeterol can also improve the MCC by increasing the ciliary beat frequency, activating the cystic fibrosis transmembrane conductance regulator and increasing epithelial permeability. However this is effect is depressed in chronic bronchitis associated with COPD and smokers. Our data indicates that cigarette smoke can interfere with the MCC enhancing property of albuterol/salmeterol by activating TGF-beta1. Coincidently, TGF-beta1 is also implicated in COPD. Thus understanding the mechanism by which cigarette smoke exposure inhibits TGF-beta1 signaling may allow us to develop therapeutics to bypass this inhibition. Simultaneously, this proposal will develop an aptamer-siRNA chimera targeting the TGF-beta signaling pathway to restore the ability of beta-2-agonists to enhance mucociliary clearance in these airway diseases. Anti-TGF-b therapeutics would also find application in lung cancer and reversing airway remodeling in COPD and asthma.

Gaofeng Wang	University of Miami	Determine smoking susceptibility loci in age-related macular degeneration.	Age-related macular degeneration (AMD) is the number one cause of legal blindness in the USA. Tobacco smoke is the strongest and most consistent risk factor for AMD. People who have smoked at least 100 cigarettes have approximately triple the risk of developing AMD compared to individuals who have never smoked. How tobacco smoke causes AMD remains largely unclear. The long-term objective is to uncover the biological role of smoking in AMD and to develop innovative therapeutic strategies to prevent and treat smoking-related damages in the retina. Specifically, this study aims to identify genes being damaged in the retina when exposed to cigarette smoke. To approach this goal, mice are chosen as a convenient model due to the ability to carefully provide a measured exposure to tobacco smoke. A similar project in humans is more difficult due to variable genomic backgrounds and inability to control tobacco exposures experimentally. Next generation DNA sequencing technology will be used to screen for DNA damages (methylation) and changes in gene expression. Initial findings of candidate smoking susceptibility loci will be further tested in a second dataset for verification. The knowledge derived from this study will unveil the effects of smoking on the genome and will be crucial for future studies to develop and test treatment or even prevent the onset of AMD in humans.

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Sion Williams	University of Miami	High resolution mapping and quantitation of somatic mitochondrial DNA variants in heart failure.	Mitochondria are cellular organelles that play an essential role in energy production. As they are involved in controlling metabolism of tissues like heart and are capable of producing oxidative damage, they are thought to play a role in role in the development and progression of heart failure. Mitochondria carry their own small genome called mitochondrial DNA (mtDNA) and around 20 years ago it was discovered that mtDNA accumulates mutations both as we age and as a result of oxidative damage due to environmental stresses like tobacco use. Because many different mtDNA mutations occur at very low frequency in a tissue, research on mtDNA mutations and has been very difficult. By applying new DNA sequencing technology we have been able to overcome these limitations and have found that a larger and more complex spectrum of mtDNA mutations is present in aging brain than was previously known. We will apply the same technology to normal and failing heart tissue to build a more accurate picture of what happens to mtDNA and mitochondrial gene expression in heart failure. As it is thought that cells accumulate mtDNA mutations randomly, we will also examine what patterns of mtDNA mutations occur in individual cardiomyocytes (heart muscle cells) that have defective mitochondria. This research will help answer long standing questions on the contribution of mtDNA mutations to the development and progression of heart failure.
Naohiro Terada	University of Florida	T3SS-MEDIATED CARDIOMYOCYTE ENGINEERING	Cigarette smoking is a major cause of coronary heart disease, which leads to heart attack. Cellular reprogramming technologies have great impact in regenerative medicine and hold tremendous therapeutic potential to replace damaged heart tissues caused by ischemia. We have recently developed minimally cytotoxic bacterial strains that can efficiently deliver reprogramming peptides into mammalian cells. The current proposal will establish an easy, affordable and safe direct-reprogramming method to engineer transplantable human cardiomyocytes, thus significantly advancing cellular transplantation therapy toward ischemic heart diseases.

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Omaida Velazquez	University of Miami	Role of the Notch Signaling in Atherosclerosis & Stem Cell-Mediated Arterial Repair	Atherosclerosis and its associated complications, including heart attack and stroke, remain the primary cause of death in humans. Smoking is one of notorious risk factors triggering artery injure that allows plaque to build up along the lining of arterial walls. We recently submitted a RO1 application to the National Heart, Lung and Blood Institute (NHLBI) and proposed to test and develop a novel stem cell-based therapy via delivery of repair-competent bone marrow cells (RC-BMC) to the atherosclerotic lesions to reverse the pathological process. The overall goal of this proposal is to investigate the involvement of Notch signaling in these processes, and to test whether Notch activity in RC-BMC can be modified to enhance healing of atherosclerotic lesions. Meanwhile, we are developing a clinically-relevant method for atherosclerotic lesion-specific repair cell delivery using nanoparticle targeting of RC-BMC to injured endothelial cells. Outcomes from the proposed work will complement our current efforts to identify novel and critical molecular and cellular targets and to develop new translational therapeutics for the treatment of atherosclerosis. Our work will also pave the way for developing a versatile platform of targeted cell delivery method for genetically specified cell-based therapeutic approach to treat not only atherosclerosis, but also many other diseases.

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Jie Wu	Moffitt Cancer Center & Research Institute	Protein Tyrosine Kinase-Phosphatase Interaction in Tumorigenesis	Lung cancer is a major cause of death in America associated with tobacco consumption. The unmet medical need in lung cancer therapy calls for better understandings of how lung cancer cells regulate their growth and survival in order to identify cancer cell-specific vulnerability and the strategies to attack it. The Myc oncogene is often overexpressed in lung cancer. While Myc promotes tumor growth, Myc overexpression also raises vulnerability because these cells become addictive to cellular mechanisms required to support the abnormal demand of the Myc function. In this study, we aim to understand how another lung cancer oncogene called Shp2 protein tyrosine phosphatase protects lung cancer cells from Myc overexpression-induced death. By understanding the mechanism, we can uncover novel targets to attack the Myc oncogene-associated vulnerability in lung cancer cells and use the knowledge to develop more effective treatment for lung cancer.

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Alexander Agoulnik	Florida International University	Vascular effects of relaxin receptor agonists	Tobacco smoking is the leading preventable cause of premature death in the United States. Smoking is an established risk factor for acute heart failure; however the treatments and clinical outcomes for patients with this disease have not changed substantially over the past few decades. Relaxin is a natural peptide normally produced in reproductive organs; it has vasodilatory and anti-fibrotic effects in heart, lung, and other organs. Recently the relaxin hormone showed favorable results in a clinical trial in patients with acute heart failure. It reduced shortness of breath, improved all-cause and cardiovascular mortality and the progression of heart failure. However, using the recombinant relaxin peptide has significant drawbacks because it is rapidly metabolized, has high production costs, must be administered intravenously, and has a risk of inducing an adverse immunological reaction. Most of these restrictions could be eliminated by the use of bioactive small molecule compounds with relaxin-like properties. The proposed project is based on our discovery of such compounds. The data indicate that the compounds have high biological activity, low toxicity, and superior stability in experiments performed in isolated cells. The current proposal is designed to confirm the biological activity of small molecules in live animals. The use of such compounds as alternatives to the relaxin hormone will have numerous benefits in treating of this deadly disease.

Miroslav Gantar	Florida International University	Enhancing the Activity of Anticancer Drugs by a Natural Product - Phycocyanin	Anticancer drugs are notorious for their harsh side effects. The objective of this project is to improve the efficacy of the currently available anticancer drugs and to allow their usage at much smaller dosage. We have previously reported on anticancer activity of C-phycocyanin, a natural, non-toxic product that was isolated from the novel cyanobacterium Limnothrix sp. 37-2-1. In our in vitro experiments, we found that when only 10% of a typical dose of the anticancer drug was combined with C-phycocyanin, the cancer cells were killed at higher rate than when this drug was used alone at full dose. Based on these findings, we suggest that C-phycocyanin can potentially improve the efficacy of the currently available anticancer drugs and therefore diminish its harsh side effects in the patient. In order to prove our hypothesis, we need additional experimental data using animal studies. For that purpose, mice will be injected with the lung cancer tumor cells and then the mice will be treated with (i) the anticancer drug alone, (ii) C-phycocyanin alone and (iii) combination of the drug and C-phycocyanin. We expect that the most significant regression of tumor will occur with the combined treatment.
Hendrik Luesch	University of Florida	Development of a scalable synthetic method for lyngbyastatin 7 as a new treatment of pulmonary diseases	Natural products show outstanding potential for the development of new drugs. We have discovered marine natural products that have extremely potent activity against a protein called elastase that is overactive in chronic obstructive pulmonary disease (COPD) and other respiratory disorders. Our data suggest that these compounds, especially the compound termed lyngbyastatin 7, have superior properties compared to an approved drug to manage elastase overactivity. We aim to generate large quantities of this potent elastase inhibitor, which is necessary for further drug development. Our goal is to demonstrate the feasibility of large-scale chemical synthesis to generate enough lyngbyastatin 7 for extensive preclinical testing.

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Robert Henning	Haley VA Hospital	Umbilical Cord Cells in Hydrogels Mend Smokers Broken Hearts/Umbilical Cord Progenitor Cells in the Treatment of Acute Myocardial Infarction	Each year 1 million Americans experience acute heart attacks (AMI) and 500,000 die from AMIs. Tobacco use is an important cause of AMIs. Smokers are 4 times more likely to develop AMIs and 3 times more likely to die from AMIs than non- smokers. 50% of MI deaths occur in people aged 35 to 69, with an average loss of 22 years of life. New treatments for smokers with AMIs are needed! We are investigating stem cells from human umbilical cord blood to limit AMI size. Since 4 million births occur each year in the US, there is a tremendous resource of umbilical cord blood stem cells (hUCBC) after newborn delivery potentially available for heart repair. Our initial results in rats with AMIs indicate that hUCBC secrete biologically active factors that limit myocardial inflammation and the size of AMIs, contribute to new blood vessels, and preserve normal heart function. However

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Alison Willing	University of South Florida	HLA Interactions with Human Cord Blood Cells in a Humanized Mouse Model of Stroke	Cerebrovascular disease (or stroke) remains the leading cause of disability and the fourth major cause of death in the United States, with tobacco use being one of the greatest risk factors. There is only onde FDA-approved treatment for stroke and many failed clinical trials. Our studies with human umbilical cord blood (HUCB) cells consistently show that these cells reduce infract size and improve functional recovery when they are injected intravenously (iv) at delayed time points after stroke onset in rodent models. However, iv delivery means these cells interact with the transplant recipients' immune system, and could alter the efficacy of the transplant or produce life-threatening side effects that necessitate immune suppression and HLA matching of donor and recipient. There is no good animal model to test these immune interactions. The objective of this research project is to use mouse model with a functioning human immune system to characterize the cellular interactions between the recipient immune cells and the HUCB cells in a model more akin to the clinical situation. In this model, it will be possible to address whether HLA matching is necessary for treatment of stroke patients, and to determine how the human cells interact with the recipient's human immune system to induce recovery. These studies will provide clinically relevant data without putting a patient population at risk.

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Donald Bolser	University of Florida	An External Device for Rehabilitation of Airway Protective Behaviors	Swallow and cough, important reflexes that protect lungs and airways are profoundly impaired after stroke, a tobacco-related disorder. Disordered swallow results in aspiration of food and liquid into the lungs, while impaired coughing reduces patients ability to clear this foreign material. Impairment of these protective reflexes is directly related to a high incidence of pneumonia after stroke. Currently, there are no effective treatments for disordered swallow and cough in patients at risk for aspiration pneumonia. The long term goal of this project is to develop and test a noninvasive device for rehabilitation of impaired swallow and cough. The device will apply a low amplitude electrical current to the neck of the patient. To this end, we will conduct preclinical studies to establish proof of concept that the device enhances cough and swallow. We also will develop a portable version of the device, similar in size and weight to a smartphone, that can be used at home by a patient. The intellectual property for this device is protected by a provisional patent application submitted by the University of Florida. All work on this project will be conducted in Florida for the benefit of all Floridians.

Geoffrey Stone	University of Miami	Novel Cancer Therapy Targeting Lung Tumors for Autophagy and Antitumor Immunity	The goal of this study is to determine whether oncolytic viral vectors can be improved as a treatment for cancer. The proposal will use a unique set of genetically engineered genes that have been shown in preliminary studies to induce immune responses against dying tumor cells. This is important because a critical roadblock in generating effective cancer immune responses is the failure to cause a strong immune response against dying tumor cells. This proposal will increase the immune responses during tumor killing and determine if this increase aids in the control of tumors in small animal models. This research has the potential to enhance oncolytic viral vector cancer therapy and optimally boost the patient's immune response so they can destroy cancer cells more effectively. The ultimate goal is to develop and evaluate in clinical trials an oncolytic virus that can boost the patient's immune cells to the point where tumors and metastases regress and immune cells control the cancer for decades without the need for chemotherapy or other treatments. Oncolytic viruses have already been tested in a number of clinical trials and therefore this technology, if successfully commercialized, is likely to advance to small-scale clinical trials fairly rapidly (3-4 years).

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Hamisu Salihu	University of South Florida	Preventing fetal body and brain size reduction in low-income smoking mothers; a randomized clinical trial	Since smoking cessation programs during pregnancy have been only partially successful, especially in low- income subpopulations, it is important to develop interventions that include a strategy to reduce the undesirable impact of smoking during pregnancy. Current low-strength folic acid prescribed to pregnant women is insufficient to compensate for depleted blood folate levels among smokers. This proposal seeks to assess the value of higher-strength folic acid (in comparison to standard of care) combined with smoking cessation program in reducing the negative effects of tobacco smoke on the fetal body and brain. Three follow-up visits are planned during which participating pregnant women will be administered questionnaires and will undergo ultrasound examinations. Maternal blood will also be collected for the testing of folic acid levels and other related substances. All study participants will be followed until delivery at which time umbilical cord blood will be collected for assessment of brain growth and development. At birth the infant's body and brain growth limits will also be measured. The two groups will then be compared to determine the effectiveness of higher-strength folic acid supplementation in improving fetal body and brain growth among smokers. This study will provide important information for subsequent follow-up of these infants to determine whether the intervention improves future intellectual, behavioral and physical development.

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Alexander Cole	University of Central Florida	Utilizing a smoking cessation program to understand how cigarette smoke exacerbates nasal carriage of Staphylococcus aureus	Nearly one in five adult Floridians smoke regularly, and thus it is of critical importance to study the effect of smoking on health concerns such as the rising incidence and severity of Staphylococcus aureus (SA) infections. SA is noteworthy because it is carried in the nose without causing any symptoms, but is easily spread to other parts of the body and between people, where it is the cause of more than 60,000 deaths per year in the U.S. Approximately 30% of healthy people carry SA in their nose at any given moment while 80% of people will carry it intermittently throughout their lives. Preliminary studies indicated that smokers carry SA in their noses at a significantly higher rate than nonsmokers, which is likely due to alterations in nasal immune function that result from chronic tobacco use. The proposed studies will combine the expertise of researchers, healthcare providers, and a smoking cessation program to determine the following: Does chronic smoking impact nasal carriage of SA in terms of incidence, duration, or bacterial load? What proteins are differentially expressed in smokers that predispose them to nasal SA carriage? Does quitting smoking help restore nasal immune function and reduce the incidence of SA carriage? It is expected that these investigations will identify key modulators of nasal defense against SA, lead to improved therapies for smokers' respiratory issues, and provide a new incentive for smokers to complete cessation programs.

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Thomas Brandon	Moffitt Cancer Center	Translating Extinction Research to Improve Pharmacotherapy for Tobacco Dependence: Intervention Development and Feasibility Trial	Varenicline is a medication that is FDA-approved for the treatment of smoking. The standard dosing schedule includes 7 days of use prior to quitting smoking. However, emerging evidence suggests that lengthening the pre-cessation use of varenicline to 4 weeks improves its effectiveness. It is believed that this occurs because varenicline blocks the satisfaction that smokers experience from nicotine. Over the 4 weeks, they reduce the association between smoking and pleasure in the environments where they smoke, and this reduces their cravings to smoking in those environments. This “extinction” process occurs naturally, but we believe that we can improve upon the process by drawing upon basic learning research on extinction, as well as other extinction therapies used to treat disorders such as anxiety. This project will include the systematic development of a brief behavioral treatment that instructs smokers in these extinction-facilitation techniques during 4 weeks of precessation varenicline use, as well a preliminary test of the feasibility of the intervention. This type of preliminary research is required before a full-size clinical trial of the intervention is proposed. Thus, the goal of this project is to set the stage for a competitive grant application to the National Cancer Institute. The proposed line of research has the potential to improve the effectiveness of varenicline and other tobacco-cessation medications.

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Chunming Dong	University of Miami	MicroRNA Regulation of Smoking Induced Endothelial Progenitor Senescence	The James and Esther King Biomedical Research Program supports research for the prevention, diagnosis, treatment, and cure of diseases related to tobacco use. Tobacco smoking increases the risk of death due to heart and vascular disease. Stem cells in the body serve important functions in the repair of the blood vessels, fighting against atherosclerosis and its sequelae, including heart attacks. This project addresses how stem cells may be injured by exposure to cigarette smoke, including research into the genetic mechanisms that may impair the functionality of these important cells. It has been shown that specific non-coding genes, named microRNAs, serve as molecular switches that regulate the expression of coding genes. We have compelling data in mice showing that specific microRNA regulatory networks control critical repair functions of stem cells and may provide a link between exposure to cigarette smoke and the development of atherosclerosis and heart disease. Based on these insights, we will use molecular techniques to rescue defective stem cells obtained from tobacco smoke-exposed mice, in order to determine whether these molecules may serve as novel therapeutic targets for the treatment of atherosclerosis. These groundbreaking studies will inspire continued research support by the National Institutes of Health (NIH), as well as investment in new therapies and job creation that will benefit the citizens of Florida.

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Jianrong Lu	University of Florida	A novel ubiquitin ligase in epithelial maintenance against tobacco smoke and lung cancer progression	Cigarette smoking is the most important risk factor for the development of chronic obstructive pulmonary disease (COPD) and lung cancer, both of which are major causes of morbidity and mortality in the U.S. and worldwide. The long-term goal of this project is to unravel the molecular mechanisms by which tobacco smoke induces these lung diseases and develop new therapeutic modalities. It has been suggested that tobacco smoke induces a cellular program known as epithelial-to-mesenchymal transition (EMT), which contributes to the pathogenesis of COPD and aggressive lung cancer. The proposed project identifies and characterizes a novel suppressor of EMT, FBXO11, in the maintenance of epithelial integrity, and aims to define the role of EMT in smoke-related lung diseases. The following specific aims will be pursued: Aim 1: To verify if FBXO11 prevents the accumulation of the key EMT-inducing protein Snail. Aim 2: To investigate whether FBXO11 protects the epithelial integrity and suppresses tobacco smoke- induced EMT in vitro. Aim 3: To define the physiological role of FBXO11 in mouse lung epithelial maintenance against tobacco smoke and lung cancer progression. The proposed research will yield greater insights into the pathogenesis of tobacco smoke-related COPD and lung cancer progression, and may identify the EMT process as important molecular targets that may be exploited therapeutically in patients with either or both of these diseases.

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Michael Kapiloff	University of Miami	Therapeutic Targeting of RSK3 in Heart Failure	Smoking is a major contributor to heart disease, the leading cause of death in the United States. Despite advances in modern medicine, death from cardiovascular diseases exacerbated by smoking such as high blood pressure and heart attacks remains high. In fact, those in congestive heart failure have about a 50% chance of surviving five years after diagnosis. There is a desperate need for new treatments for heart disease. The Kapiloff laboratory has been studying the changes that occur in the heart when subject to disease. A new enzyme has been identified that although present in the normal heart muscle cell is dispensable for normal heart function. This enzyme called RSK3 is an important mediator of the changes that are part of heart disease, and genetically modified mice lacking RSK3 are protected against heart failure. A unique characteristic of RSK3 is that it is associated with another protein called mAKAP that is also important for heart disease. Using a novel therapeutic approach, the Kapiloff laboratory has acquired evidence that separating RSK3 from mAKAP in heart muscle cells prevents RSK3 from contributing to abnormal heart function. This grant will test this new idea in mice that are caused to have heart disease. In addition, RSK3 will be studied at a molecular and cellular level in order to understand how RSK3 contributes to abnormal function. Together these studies should inspire new therapies for heart disease.

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Teng Ma	Florida State University	Translation of Human Mesenchymal Stem Cell Therapy for Stroke Treatment: Bioreactor Expansion, Functional Activation, and Intranasal Delivery	In the US, stroke is the third leading cause of death and primary cause of severe disability, with over 700,000 individuals experiencing an ischemic episode each year. In Florida, the prevalence of stroke reported in 2007 is 3.1% and is higher than the national prevalence of 2.6%. Additionally, many Floridians have high blood pressure, diabetes, elevated cholesterol, or are cigarette smokers or obese, which are risk factors for stroke. Reducing morbidity and mortality from stroke has significant impact on the health of Floridians. The only FDA-approved drug for stroke is tissue plasminogen activator, a thrombolytic agent that must be infused within 4.5 h of the initial ischemia and is only beneficial in ~40% of acute cases inside this window; fewer than 5% of US patients suffering an ischemic stroke receive this treatment. We propose to advance mesenchymal stem cell (hMSCs) therapy for stroke based on promising preclinical and clinical results. The project will address the main translational barriers in the production of clinically competent hMSCs and optimization of cell delivery routes by developing a novel clinical bioreactor system for hMSC expansion and by demonstrating therapeutic outcome of intranasal hMSC delivery in stroked rat model using the FDA-accepted behavior measures. By the end of this project, we will be able to produce clinical grade hMSCs and determine the feasibility and efficacy of intranasal hMSC delivery.

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Maria Jose Miguez	Florida International University	Menthol or Not menthol: How Smoking is related to Bone Mineral Density in People With and Without HIV	In the United States over half of individuals 50 years and older will be diagnosed with osteoporosis, and this frightening rate is even greater in people living with HIV (PLWH). These statistics are of concern because osteoporosis is known for carrying significant morbidity and mortality risks. Indeed, it has been estimated that osteoporosis will cost Florida two billion dollars. This public health threat may be further complicated by smoking, which our group has demonstrated is widespread in this population in Florida. Noteworthy, our analyses uncovered a conglomeration of factors associated with poor bone health among users of mentholated cigarettes. Although osteoporosis is at the forefront of medical concerns, an important, yet unknown issue for clinicians and public health authorities is whether mentholated cigarettes heighten skeletal health risks. Unfortunately, smokers and/or PLWH are not always aware of their enhanced risks, and thus do not recognize the need to take preventive actions. Thus, our second goal is to rigorously examine if bone health screening results can be used as "cue to action" to enhance knowledge and bone health through lifestyle modifications, including stopping smoking, consuming a more healthy diet, and engaging in exercise.

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Linda Hayward	University of Florida	Impact of nicotine exposure on prenatal infection and a lifelong predisposition for cardiovascular disease	Cigarette smoking is highly addictive and has both short-term and long-term deleterious effects on human health. During pregnancy, maternal smoking is one of the major risk factors for spontaneous abortion, prematurity and low birth weight of infants. Novel preliminary data from our research group now demonstrate that exposure to nicotine during pregnancy also increases intrauterine infection rate. Intrauterine infection, like prenatal nicotine exposure, is a major risk factor for adverse pregnancy outcome. The focus of the proposed research to evaluate the relationship between varying levels of prenatal nicotine exposure on the transmission of maternal infection to the fetal environment and impact perinatal development. This research will directly impact the treatment of women smoking or looking for therapeutic options to quit smoking during pregnancy and will clarify minimum dosing strategies used for nicotine replacement therapy during pregnancy. The outcome of this study will also identify whether health care policies for monitoring infection during pregnancy in smokers should be implemented. Finally, this research will identify for the first time whether adults exposed to both prenatal nicotine and infection are also at an increased risk for cardiovascular disease. Overall, the outcome of this research will significantly advance our understanding of the nicotine exposure in utero and should lead to significant changes in health care delivery and outcome monitoring.

Jiandong Chen	Moffitt Cancer Center	Nucleolar silencing and maintenance of cellular senescence	Chemotherapy causes tumor shrinkage through several mechanisms. Some tumors undergo cell death, which is the most desirable outcome. However, many tumors have developed resistance to cell death. Treatment of such tumors may induce cellular senescence in which cells stop proliferating. Such cells may be removed by the immune system or remain dormant, resulting in a stable disease state that is desirable over tumor progression. However, studies using lung tumor cells showed that rare cells can bypass entry to senescence, or re-enter proliferation from a senescent state, thus causing resistance to treatment or rapid relapse of tumors after chemotherapy. Understanding the regulation of senescence induction and escape may lead to new strategies to prevent or delay tumor relapse after therapy. Senescence involves turning off cell proliferation genes and reducing protein synthesis rate. This project will investigate how proteins that controlling genes in protein synthesis can affect the ability of cells to undergo senescence and revert to proliferation from a senescent state. The experiments will analyze the molecular mechanisms of gene regulation by a nucleolar protein (NML), and use a new drug to test whether more robust senescence arrest can be achieved in a lung tumor xenograft model. The experiments will lead to better understanding of the role of nucleolar transcription in drug response, and develop a novel therapeutic strategy by targeting the nucleolus.

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Ana Palacio	University of Miami	Improving Adherence to Cholesterol Lowering Medications among Minority Populations in Florida: A Randomized Trial	Heart disease is the leading cause of death in the US. In addition, Hispanics and blacks suffer disproportionately from this disease. Taking a cholesterol lowering medications (also known as “statins”) significantly reduces the risk of heart disease. Unfortunately, only half of patients started on a statin continue taking it for one year. Adherence is particularly suboptimal among minorities which may contribute to racial disparities in heart disease. With support from the James and Esther King research program, we are conducting a study to determine if a culturally tailored phone based behavior modification intervention (also known as Motivational Interviewing, MINT) can improve adherence to statins among minorities living in Florida. To date we have recruited 636 of our planned 800 Black and Latino subjects into our study. Once all subjects have completed the one year follow-up period, we will use pharmacy claims data to determine if those subjects receiving MINT had better medication adherence than those receiving usual care. Although our study had been approved for five years, we were recently notified that we would need to submit a new proposal to complete years 4 and 5 of our study. This would allow us to complete the study and conduct the analysis. We would then be able to determine if the intervention succeed in improving adherence to a medication that may play a large role in reducing heart disease among minorities in Florida.

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Bruce Citron	Bay Pines VAHCS	Preventing oxidative neurodegeneration after traumatic brain injury	Traumatic brain injury (TBI) is increasingly common and can be caused by a variety of events, including vehicular accidents and falls, and is also a frequent occurrence among recently deployed military personnel. TBI typically results in neurodegeneration and cognitive deficits and there is no effective treatment available. Oxidative damage in the brain is caused by the traumatic brain injury and is also caused by exposure to tobacco smoke. There are clues that the effects of tobacco smoke and the injury combine to accelerate degradation. Experiments, with a mouse model system, to quantitatively define the effects of TBI with and without smoke exposure followed by measurements of cognitive performance, neurodegeneration, and connectivity within the brain will aid our understanding of the harm of tobacco smoke on TBI recovery. This knowledge will advance preventative anti-smoking efforts and help Floridians and others make better health choices. A treatment to elevate antioxidant processes in the brain will also be tested after TBI with and without tobacco smoke exposure to identify the benefits of the treatment to smokers and also to non-smokers. In summary, prevention will be promoted and the therapeutic experiments to combat the neurodegeneration produced by these insults will advance treatment for those suffering TBI for all patients, and the discovery of an effective therapeutic anti-neurodegenerative target will also have implications for other disorders.

Monica Webb Hooper	University of Miami	Addressing Racial/Ethnic Tobacco Health Disparities via Group Intervention	The importance of reducing tobacco-associated health disparities between cannot be understated. Racial/ethnic minorities are less likely to quit smoking, and tend to have elevated stress and depressive symptoms, which may contribute to cessation disparities. Cognitive behavioral therapy (CBT) for cessation addresses these concerns and has the potential to reduce/eliminate disparities. Our preliminary research found racial/ethnic differences in baseline perceived stress and depressive symptoms. Following CBT, these differences were no longer present. Moreover, compared to Whites, African Americans exhibited blunted hypothalamic-pituitary-adrenal (HPA) axis functioning. This RCT will be the first to test the impact of CBT on smoking cessation disparities. Our specific aims are to: (1) Examine the effects of CBT on perceived stress and depressive symptoms in a racially/ethnically diverse sample; (2) test the efficacy of CBT for eliminating smoking cessation disparities; and (3) examine physiological distress as an underlying mechanism for the effects of CBT on racial/ethnic minority smokers (exploratory). We expect that CBT will eliminate racial/ethnic differences in stress and depressive symptoms, and smoking cessation compared to the general health education (GHE) control group. We also hypothesize that HPA functioning will mediate the effect of CBT on smoking cessation, particularly among racial/ethnic minorities. We will randomly assign African American/Black, Hispanic, or White smokers to CBT or GHE, and provide transdermal nicotine patches (TNP) to both intervention groups. Assessments will occur at the end-of-therapy (EOT), and 3, 6, and 12-months. Our primary abstinence outcome will be smoking cessation over the previous 7 days. We will also examine the effect of CBT on TNP adherence. This study has implications for eliminating disparities in psychosocial factors related to smoking cessation, and disparities in quitting success. Addressing stress and depressive symptoms through CBT may facilitate cessation, particularly among racial/ethnic minorities.
Matthias Salathe	University of Miami	Adverse airway effects of inhaled nicotine from tobacco and e-cigarettes	In healthy persons, the lungs and airways are cleared from dust, viruses and bacteria to prevent disease development. Cigarette smoke impairs these host defense systems, allowing mucus build up, which is revealed by cough productive of phlegm and associated with frequent infections. This leads to diseases called chronic bronchitis and COPD. From a public health perspective, smoking cessation is therefore an important goal. To try to decrease nicotine craving during smoking cessation, tobacco-free nicotine delivery devices such as electronic cigarettes (ECs) are used. However, the safety of inhaled nicotine via ECs is unknown. In the present study, we will first use human cells that represent the airway surface in a dish and expose them to smoke to study the mechanism by which smoke components, especially nicotine, cause changes leading to increased sputum production. Our preliminary results show that the inflammatory molecule TGF-β1 is responsible for many of these changes and that inhibition of this molecule's signaling can prevent mucus build up. We will test whether nicotine directly or delivery via ECs causes changes similar to tobacco smoke in vitro. Next, we will examine whether changes observed in vitro also occur in vivo in human beings. We will test whether subjects who quit smoking with ECs show toxic effects from nicotine delivered to their airways or whether such a strategy is safe. Therefore, this translational research project will examine treatments to reverse smoking effects on the airway epithelium and will comprehensibly examine whether the delivery of nicotine via ECs has detrimental effects as well. The outcome of this project will not only be important for subjects with smoke-induced lung diseases,

			but will also provide a decision making basis for subjects and policy makers how to use and regulate nicotine delivery devices such as ECs.
Vani Simmons	H. Lee Moffitt Cancer Center and Research Institute	Expanding the reach of a validated smoking-cessation intervention: A Spanish-language clinical trial	Tobacco smoking is the leading preventable cause of cancer mortality. Pharmacotherapy and behavioral counseling have demonstrated independent and additive effects on smoking cessation rates; however, counseling is rarely chosen by smokers. Minimal self-help interventions, such as smoking cessation booklets, have very high potential reach, yet have shown low efficacy, with the exception of the extended self-help smoking interventions developed by our research team. Originally developed to prevent post-cessation relapse to smoking, these booklets titled, Forever Free, significantly reduced smoking relapse through two years of follow-up among individuals who had recently quit smoking and were extremely cost-effective. Based on its efficacy and cost-effectiveness, we expanded the intervention to assist current smokers with initial smoking cessation as well as relapse prevention. Our recently completed National Cancer Institute funded trial of this intervention titled, Stop Smoking for Good, revealed high efficacy through the 24-month follow-up, further supporting the utility of extended self-help for promoting and maintaining tobacco abstinence. Availability of a validated Spanish-language version would enhance its public health impact by reaching the largest and fastest growing ethnic minority population of smokers. Although the current smoking prevalence among Hispanics (12.5%) is lower than non-Hispanic whites (18.1%), higher prevalence is observed among certain subgroups (e.g., Puerto Rican males, 35%). In Florida, the smoking prevalence among Hispanics (15.1%) is greater than the national prevalence, and it is higher among subgroups and within medically underserved communities. Prior work has demonstrated that Hispanic smokers face unique challenges such as lower awareness and acceptance of pharmacotherapies and less cessation assistance from health providers. This study goal is to expand the reach of our evidence-based, self-help intervention by developing and testing a Spanish-language version. This would represent an easily disseminable, low-cost intervention with significant public health impact for Hispanic smokers in Florida and elsewhere.

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Frederic J. Kaye	University of Florida	First-of-its-Kind Intralesional Delivery of Oncolytic therapy for Limited Stage Small Cell Lung Cancer	Small cell lung cancer (SCLC) is a unique and highly aggressive subtype of lung cancer that rapidly spreads to distant organs and for which there have been no improvements in standard treatments for the past 3 decades. SCLC is also the subtype of lung cancer that is most tightly linked with tobacco use and will kill almost 26,000 patients in the U.S. in 2013. Therefore, there is a great need for new therapeutic strategies. We now propose a new team science project to exploit Myxoma virus (MYXV) as a novel viral-based therapeutic that is harmless for normal human tissues but targets and kills SCLC. Projects 1 and 2 will take advantage of our unique resources of i) a large collection of human SCLC tumor samples for testing and optimizing the killing of tumor cells in the laboratory and in specialized animal models, ii) a new genetically engineered SCLC mouse model for further confirmation of safety and efficacy testing, iii) our expertise in optimizing MYXV to enhance immune-mediated cell killing to maximize our ability to cure this disease, and iv) our promising preliminary data already showing efficient MYXV infection and cell killing of human and mouse SCLC in vitro and in vivo. Project 3 focuses on a pioneering clinical program in navigational and interventional bronchoscopy that is only available at the University of Florida and which allows for studying the efficacy of MYXV on fresh SCLC samples with plans for future investigator-initiated clinical trial using intralesional delivery of this therapy. We are making a strong effort to develop tobacco-related SCLC as an important topic for clinical and translational research in the state of Florida.
Chen Liu	University of Florida	Novel small molecules for alpha-1 antitrypsin deficiency.	The alpha-1 antitrypsin (AAT) deficiency is a common genetic disease with pulmonary emphysema and chronic obstructive pulmonary disease (COPD), for which there is no effective treatment. Smoking tobacco is the single most important risk factor to accelerate the lung disease. The fundamental pathological process is that the accumulation of mutant AAT in the form of polymers within hepatocytes causes low levels of AAT in the serum, resulting in lung tissue damage by proteinases. AAT is the second most abundant protein in the blood. A effective method to treat COPD is to stop AAT forming multiple chains in the liver and allow the protein coming out. Secretion of the protein may simultaneously alleviate both the liver and the lung diseases. Protein structural analysis have identified the site responsible for AAT polymerization (chains). This site is an attractive target for drug design. We think that specific small molecules that interfere with AAT polymerization can be identified by a molecular docking approach and these small molecules can be developed into novel therapeutic drugs. We have used computer-based molecular docking program and the NCI/Developmental Therapeutics Program (NCI/DTP) depository to identify promising compounds that demonstrate efficacy to enhance secretion of AAT protein. We have obtained US patent for these molecules. Our objective is to develop these small molecules into clinical useful drugs. In this proposed study, we will test and validate these compounds in cell and animal models. The preclinical study will be the scientific basis for subsequent clinical trials.

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Doug Cress	H. Lee Moffitt Cancer Center and Research Institute	Proliferative signatures to predict the benefit of Adjuvant Chemotherapy in Early-Stage non-small cell lung cancer	Stage 1 lung cancer patients have only a 50% chance of surviving for five years. We believe that many of these patients should be treated more aggressively than is currently recommended. Since 2010, these patients are treated surgically and are released, based on evidence that the group as a whole, does not benefit. However, since HALF of them will recur and die we can surmise that many were not cancer free after surgery. These might have benefitted from adjuvant (given after surgery) chemotherapy, but in the past there was no way to tell which patients would benefit. Recognizing this problem, we have identified a genetic signature that may identify early-staged tumors that have deadly potential. We have developed our signature into a relatively simple and inexpensive test based on NanoString barcode technology. This test can be used on standard pathology sides (even if they are decades old).It would be very expensive to prove that our test works by conducting a clinical trial in which patients would be randomized into two arms. Fortunately, the trial has already been done, in two ways. First, a study was published in 2010 by the Spanish Lung Cancer Group that essentially performed the definitive clinical trial on treatment decisions for early staged lung cancer and they have provided the pathology slides from 223 of those patients. Second, we have utilized our access to samples from Floridian-based patients to identify a cohort of about 399 patients one-third of which were treated with ACT. We will also perform mutational analysis on these cohorts. We will use these two cohorts to further prove that our test works and validate how well it works in combination with other predictors such as mutation analysis.